REMARKS

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Status of Claims

Claims 1, 3, 4, and 6-10 are pending in the application. Claims 1, 3, 4, and 6-10 have been rejected. Claims 1,3 and 4 have been amended.

Claims 2 have been canceled without prejudice or disclaimer. In making this cancellation without prejudice, Applicants reserve all rights in these claims to file divisional and/or continuation patent applications.

The Telephone Interview

Initially, Applicants wish to thank the Examiner, Blessing M. Fubara, for granting and attending the telephone interview, with Applicants' Representative, Mark Treitel, Reg. No. REG. NO. on 27 June, 2007. In the interview, the written description was discussed. Applicant stated that the Lactide or PLGA in combination with 20-40% Haloperidol provided unexpected release rate or profile, as disclosed on page 9, lines 7-12 of the present Application and proposed amendment would overcome the prior art cited (Mao et al., US Patent No. 6,166,173 – The '173 Patent). In the '173 Patent the Polymer has a phosphate group that, as agreed to by the Examiner, is not present in the polymer of the present invention. The Examiner further agreed to consider arguments to that effect when the amendment is filed.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103

In the Office Action dated October 19, 2006, the Examiner rejected claims 1, 3, 4, and 6-10 under 35 U.S.C. § 103(a), as being allegedly unpatentable over Mao et al., in the '173 Patent. The Examiner alleged that Mao disclosed: (a) biodegradable medical implant devices that incorporate 1-65% active agent; (b) that any antipsychotic drugs (e.g. clozapine,

haloperidol, and risperidone) can be used; and (c) use of lactic acid copolymers. The Examiner alleged that "The difference... between Mao and the instant claims is [only] the amount of the haloperidol" (October 19, 2006 Office Action page 3, first full paragraph). Therefore, Examiner alleged that it would have been obvious to modify the implant of Mao to arrive at the implants claimed in the subject claims.

In response dated March 8, 2007, Applicants pointed out to the Examiner that the polymers in the subject application are different from those claimed in the '173 Patent, in that the polymers in the '173 Patent contain a phosphate ester linkage, which is not present in either polylactide or lactide-co-glycolide copolymers; and the phosphate ester materially changes the basic characteristics of thereof, e.g. the degradation pattern, drug/polymer interaction and the ability to incorporate an active compound into the polymers (i.e. loading).

In a telephone interview conducted on June 27, 2007, the Examiner agreed that the phosphate linkage is not present in the polymer of the present invention. The Examiner further agreed to consider arguments to that effect when the amendment is filed.

Applicants' amended claim 1 recites a surgically implantable drug delivery system comprising a biodegradable polymer or copolymer *consisting essentially of* polylactide or lactide-co-glycolide copolymer and 20 to 40% haloperidol fabricated into an individual, surgically implantable implant via solvent casting and compression molding at a temperature and pressure which allows the haloperidol-polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more and is removable from the patient in the event the patient exhibits unwanted side effects following implantation. Likewise, Applicants amended claim 4 to recite a method of producing an individual, surgically implantable implant which is surgically implanted underneath the skin of a patient for delivery of steady state concentrations of haloperidol to the patient for 5 months or more comprising: (a) dissolving haloperidol and a biodegradable polymer *consisting essentially of* polylactide or lactide-co-glycolide copolymer in acetone; (b) solvent casting the haloperidol and biodegradable polymer solution to produce a completely dry haloperidol-polymer material; and (c) molding under compression the dry haloperidol-polymer material at a temperature and pressure which allows the haloperidol-

polymer material to flow into a mold for the individual, surgically implantable implant which is surgically implanted underneath the skin of a patient, delivers steady state concentrations of haloperidol to the patient for 5 months or more, and is removable following implantation into a patient in the event the patient exhibits unwanted side effects following implantation.

The '173 Patent does not consist essentially of polylactide or lactide-co-glycolide copolymer. Rather, as described in more detail hereinbelow, (a) the polymer of Mao contains phosphate ester linkages; and (b) the presence of phosphate ester linkages in the polymer of materially affects the basic and novel characteristics of the invention; namely, the release profile, degradation rate and loading of the implants.

a. The subject Application demonstrates that release rate of the implants constitutes a basic characteristic of the claimed implants

Specifically, the subject Application states:

> "The surgically implantable preparations of the present invention are designed to last for months to years" (subject specification page 7, lines 33-34).
>
> "Haloperidol released from the bioerodible implant of the present invention maintains its bioactivity and is delivered at steady state concentrations to the patients for periods of five months or more" (page 13, lines 11-15).

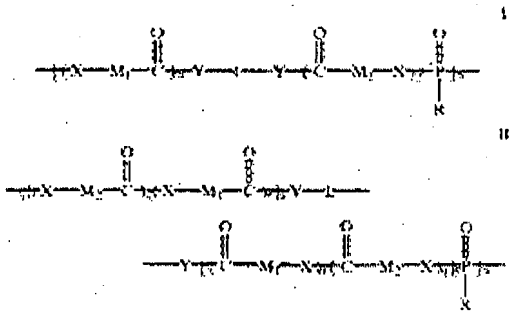
Thus, the subject Application clearly shows that Applicants consider release profile of the implants to constitute a basic characteristic of the claimed implants. In view of this teaching of the subject specification, the basic characteristics of the polymer disclosed in the '173 Patent are materially different from the claimed implants of the subject invention. Accordingly, the polymer disclosed in the '173 Patent is excluded by the phrase "consisting essentially of polylactide or lactide-co-glycolide copolymer" in the subject claims.

In addition, the polymers in the '173 Patent differ from those of the present invention in that the polymers in the '173 Patent contain a phosphate ester linkage, which is not present in either polylactide or lactide-co-glycolide copolymers; and the phosphate ester linkages

materially change the degradation pattern of the implants, its loading capabilities and release profile.

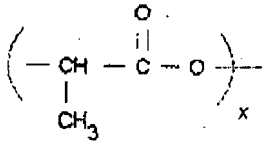
b. Polymers in the '173 Patent differ from those of the present invention in the presence of a phosphate ester linkage

The polymers in the '173 Patent have 1 of the following formulas:



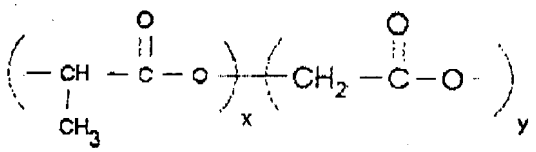
As clearly depicted on the right side of each of the above structures, these polymers contain phosphate esters.

By contrast, polylactide and lactide-co-glycolide copolymers of the subject invention do not contain a phosphate linkage. Polylactide polymers have the formula:



Lactide-co-glycolide copolymers have the formula:

$$[OCH(CH_3)CO]_x[OCH_2CO]_y$$



No phosphate is present in either of the above formulas.

Further, the alleged disclosure of polylactide and lactide-co-glycolide copolymers in columns 12-13 in the '173 Patent is limited, as clearly stated in column 12, line 50 in the '173 Patent, to the use of polylactide and lactide-co-glycolide copolymers as reagents ("prepolymers") for use in step (b) of the synthesis reaction described in column 11, lines 44-55 in the '173 Patent. The purpose of step (b) is to create "interconnecting phosphorylated units" (column 13, lines 36-37). The cited passage does not disclose or contemplate the use of the unmodified prepolymers. Accordingly, the disclosure in the '173 Patent teaches nothing about polymers that do not contain a phosphate moiety; e.g. polymers of the present invention.

c. The phosphate ester linkages in the '173 Patent materially change the degradation pattern of the implants

In addition, the '173 Patent discloses that the phosphate linkages affect the release rate of the polymers disclosed therein:

> "The polymers of formulas I and II are usually characterized by a release rate of the biologically active substance *in vivo* that is controlled at least in part as a function of hydrolysis of the phosphoester bond of the polymer during biodegradation" (column 14, lines 25-36; emphasis added).

Thus, the '173 Patent teaches that the phosphate moieties affect the drug release rate.

Accordingly, in view of the teaching of the present Application's specification indicating that the release rate of the claimed implants constitutes a basic characteristic of the claimed invention, as described hereinabove, the polymer in the '173 Patent is materially different from the claimed implants in its basic characteristics. Accordingly, the polymer in the '173 Patent is excluded by the phrase "consisting essentially of polylactide or lactide-co-glycolide copolymer" in the subject claims, thus distinguishing the polymers in the '173 Patent from those of the present invention

d. The '173 Patent teaches away from removal of the phosphate group

Further, the '173 Patent teaches against removal of the phosphate group, by teaching that the phosphate group is critical for the biological functionality.

For example, the '173 Patent disclosed in column 14, lines 25-36 that the phosphate linkages affect the release rate of the polymers disclosed therein, as quoted hereinabove.

Further, the '173 Patent indicates that the presence of the phosphate group confers ability to incorporate an active compound into the polymers disclosed therein:

> "Additionally, the biologically active substance to be released may be conjugated to the phosphorus sidechain R' to form a pendant drug delivery system" (column 14, lines 36-38).

In summary, The '173 Patent teaches that the phosphate moieties present in the implants disclosed therein are important both in incorporation of a drug into the polymer and in determining the drug release rate. Since the '173 Patent discloses that the phosphate group is central and critical to the claimed functionality, a person skilled in the art would not remove the phosphate from the polymers in the '173 Patent and/or replace it with another moiety. Doing so would completely alter the polymers and resulting implants from the entire disclosure of the invention. Clearly, the '173 Patent further teaches against removing the phosphate moieties from the polymers in the '173 Patent, thus providing yet another reason why the implants of the present invention are not obvious in view in the '173 Patent.

e. Unexpected properties of the 20-40% range

As mentioned hereinabove, the Examiner alleged that "The difference... between The '173 Patent and the instant claims is [only] the amount of the haloperidol" (page 3, first full paragraph of the October 19, 2006 Office Action). Therefore, Examiner alleged that it would have been obvious to modify the 1-65% active agent range disclosed in The '173 Patent to arrive at the implants of the present invention, which contain 20-40% haloperidol.

Applicants respectfully disagree. In making the above assertion, the Examiner has ignored the unexpected finding by Applicants, showing a decreasing release rate with increasing drug percentage; as disclosed in the subject specification:

> "Haloperidol concentrations preferably range from about 20% to about 40% in the delivery system depending upon the release period. Inclusion of haloperidol in the drug delivery system actually increases the stability of the

drug delivery system. Thus, the higher the concentration of haloperidol, the more extended the period of release" (page 9, lines 7-12).

The above surprising property of implants of the present invention was not disclosed or suggested for any of the implants in the '173 Patent, thus providing yet another reason why the implants of the present invention differ from those in the '173 Patent and are not obvious in view in the '173 Patent.

Moreover, there is no support in the '173 Patent for drug loading beyond 7.6% of Lidocain (See Example 12, Col. 27, lines 31-35). The FITC-BSA loading is of a model protein used, not a drug and even with FITC-BSA, maximum loading obtained was 24.98% (Col. 26, line 15), nor support for steady state release over a period of 5 months, since the implants demonstrated in the '173 Patent show 100% release of lidocain over a period of no more than 16 days (See Figure 16).

f. Superior steady-state release properties of implants of the present invention

As demonstrated in the subject Application, implants of the present invention exhibit steady-state release for 5 months or more:

"Haloperidol released from the biocrodible implant of the present invention maintains its bioactivity and is delivered at steady state concentrations to the patients for periods of five months or more" (p. 13, lines 13-16).

This additional difference between the claimed implants and those in the '173 Patent was not disclosed or suggested for any of the implants in the '173 Patent, thus providing yet another reason why the implants of the present invention differ from those in the '173 Patent and are not obvious in view in the '173 Patent.

g. Removability of implants of the present invention

Further, as demonstrated in the subject specification, implants of the present invention are removable, as demonstrated by reversal of *in vivo* effects on locomotion:

> "After apomorphine challenge, animals that had control implants traveled a mean of 4721 ± 476 cm, while those with haloperidol containing implants traveled a mean of 8531 ± 2536 cm. Therefore, following removal of implants and exposure to apomorphine, mice that had haloperidol implants traveled more distance than control mice ($p<0.02$)" (p. 11, lines 8-11).

This additional difference between the claimed implants and those in the '173 Patent was not disclosed or suggested for any of the implants in the '173 Patent, thus providing yet another reason why the implants of the present invention differ from those in the '173 Patent and are not obvious in view in the '173 Patent.

h. Lack of enabling disclosure for haloperidol-containing implants in The '173 Patent

Regarding haloperidol, as mentioned hereinabove, the Examiner alleged that The '173 Patent disclosed the use of any antipsychotic drugs (e.g. clozapine, haloperidol, and risperidone) with the proposed implants.

In response, Applicants have previously pointed out to the Examiner that haloperidol is disclosed as part of a very large list encompassing hundreds of different active compounds (of the 129 items listed, many items are actually classes of compounds, each of which may contain several to dozens of known active compounds), without providing any guidance as to which of the compounds would likely work in the implants disclosed therein, or without providing enablement of any of the compounds on the list.

In response to Applicants' arguments, the Examiner alleged in the Advisory Action that the listing of antipsychotic drugs is limited to three- clozapine, risperidone, and haloperidol, and thus does not represent a "laundry list."

Applicants respectfully disagree. The number of antipsychotic drugs disclosed in The '173 Patent does not change the fact that The '173 Patent provides no guidance as to which of the hundreds of total compounds listed would likely work in the implants disclosed therein and provides no enablement of combining any of the compounds in the list with the implants disclosed in The '173 Patent. Further, a person skilled in art knew that a mere suggestion to

combine a drug with a particular polymer does not provide enablement in the absence of data for the particular drug, as shown, for example, in the teaching of the subject specification that thiothixene behaves completely different from haloperidol in implants of the present invention:

> "Inclusion of haloperidol in the drug delivery system actually increases the stability of the drug delivery system. Thus, the higher the concentration of haloperidol, the more extended the period of release. This increase in stability does not occur with all drugs. In fact, other antipsychotic drugs such as thiothixene decreased stability and the period of release of the drug delivery system when drug concentrations were increased" (page 9, lines 11-16).

Moreover, as Applicants provide in the present invention, (see *See* e.g. US Publication 20020179096, pp. 4, Para 30

> "Interestingly, not all pharmaceutical agents nor all antipsychotic agents are amendable to this delivery system. For example, incorporation of the antipsychotic agent thiothixene into the implant requires lowering of the molding temperature by 40°C. and causes an acceleration in degradation of the polymer as opposed to an extension of degradation time as observed with haloperidol. Further, implant comprising thiothixene degraded at room temperature without exposure to an aqueous environment within 6 months. These implants discolored to a yellow shade and liquefied. In contrast, haloperidol implants ... are stable in storage for periods exceeding one year without any signs of discoloration or change in consistency. Incorporation of the anti-depressant Fluoxetine into this delivery system resulted in an implant which caused tissue necrosis in 8 out of 8 mice tested. No tissue necrosis was observed in mice with control, Navane loaded or haloperidol-loaded implants"

Thus, The '173 Patent does not provide an enabling disclosure of a combination of haloperidol with the implants disclosed therein.

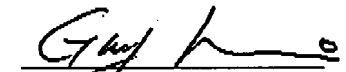
An obviousness rejection requires a teaching or a suggestion by the relied upon prior art of all the elements of a claim (M.P.E.P. §2142). The cited prior art, does not teach or suggests all the claim elements as recited in Applicants' amended independent claims 1 and 4. Thus, the Examiner's grounds for rejection are insufficient. Accordingly, Applicants respectfully request withdrawal of the rejection

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,



Mark S. Cohen Registration No. 42,425
Guy Levi Registration No. 55,376
Attorney/Agent for Applicant(s)

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Pearl Cohen Zedek Latzer, LLP
1500 Broadway, 12th Floor
New York, New York 10036
Tel: (646) 878-0800
Fax: (646) 878-0801